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Letter to the Editor

Serum gamma-glutamyltransferase is associated with future risk of psychosis - a prospective cohort study

Setor K. Kunutsor [a, *] and Jari A. Laukkanen [b,c]

[a] *School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, UK*

[b] *Institute of Public Health and Clinical Nutrition, University of Eastern Finland, Kuopio, Finland*

[c] *Central Finland Central Hospital, Jyväskylä, Finland*

[*] Corresponding author at: School of Clinical Sciences, University of Bristol, Learning & Research Building (Level 1), Southmead Hospital, Southmead Road, Bristol, BS10 5NB, UK. Phone: +44-7539589186; Fax: +44-1174147924; Email address: skk31@cantab.net

Psychosis is a severe mental illness which is characterized by distortion of reality (delusion and hallucination); disorganized thought or language; and markedly abnormal psychomotor behaviour (such as stupor and mutism). Psychotic disorders remain a vast public health burden and are associated with significant disability and morbidity, high societal costs, as well as mortality.(McGrath et al., 2008) Well known risk factors for psychosis include family history, gender, abnormal foetal development, neurodegenerative diseases, and socioeconomic factors.(Benros et al., 2011; Heckers, 2009) Though these factors significantly elevate the risk for psychosis, they do not fully explain its pathogenesis.

Psychosis is a preventable mental illness and therefore there is a need to evaluate putative risk factors that may contribute to its development. Gamma-glutamyltransferase (GGT), a known marker of liver injury, has been implicated in the development of a vast array of chronic disease outcomes;(Kunutsor, 2016) via pathways related to inflammation and oxidative stress. Emerging evidence also suggests that inflammatory processes may be involved in the etiopathogenesis of psychosis.(Feigenson et al., 2014) We therefore hypothesized that GGT will be linked to the development of psychosis. In this context, we aimed to assess the association of GGT with risk of psychosis, using a population-based cohort of 2,341 men free from any apparent mental illness at baseline from eastern Finland.

Study population comprised a representative sample of middle-aged men aged 42-61 years recruited into the Finnish Kuopio Ischemic Heart Disease (KIHD) risk factor study.(Salonen et al., 1992) The Research Ethics Committee of the University of Eastern Finland approved the study, and each participant gave written informed consent. Men on antipsychotic medication (n=52) were excluded at baseline. Serum GGT activity was measured at baseline using the kinetic method (Thermo Fisher Scientific, Vantaa, Finland) with repeat measurements performed several years apart in a random subset of participants. Data on hospitalization due to a psychotic disorder were ascertained by linkage to the National Hospital Discharge Register. Diagnoses of psychotic disorders were made by qualified psychiatrists according to ICD-8 (290-299), ICD-9 (290-299), and ICD-10 (F00-F09 and F20-F29) codes. Hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated using Cox proportional hazard

models. All statistical analyses were conducted using Stata version 14 (Stata Corp, College Station, Texas).

The mean age [standard deviation (SD)] of participants at baseline was 53 (5) years. The median (interquartile range) baseline GGT activity was 20 (15-33) U/L. During a median follow-up of 24.7 years, 230 hospital diagnosed psychotic disorders were recorded. In analysis adjusted for conventional risk factors (age, body mass index, smoking status, history of diabetes, prevalent history of coronary heart disease, years of education, total cholesterol, and alcohol consumption), there was a log-linear association between GGT and risk of psychosis (**Figure**). The age-adjusted HR for psychosis per 1 SD increase in GGT was 1.52 (95% CI: 1.34 to 1.73), which was minimally attenuated to 1.44 (95% CI: 1.25 to 1.66) on further adjustment for established risk factors. The association remained consistent on additional adjustment for potential confounders 1.43 (95% CI: 1.24 to 1.65). After correction for within-person variability in GGT values, the similarly adjusted HRs were 1.84 (95% CI: 1.53 to 2.21), 1.70 (95% CI: 1.39 to 2.08), and 1.67 (95% CI: 1.36 to 2.06) respectively (**Table**).

In this population of approximately healthy middle-aged Finnish men, our results show a positive and independent association between GGT and future risk of psychosis, which was consistent with a graded dose-response pattern. Over the last few decades, emerging evidence suggests that chronic inflammatory processes (Benros et al., 2011; Feigenson et al., 2014) as well as oxidative stress (Owe-Larsson et al., 2011) may be involved in the pathogenesis of psychotic disorders. Whether GGT has a direct role in the pathogenesis or may just be a marker of underlying pathology, is not clear. However, given that GGT has been suggested to contribute to the development of chronic disease outcomes mainly via inflammation (Anderson et al., 1982) and oxidative stress;(Lee et al., 2004) we postulate that these same pathways might underlie the current findings.

This is the first prospective evaluation of the association between GGT and risk of psychosis using a large-scale population-based prospective general cohort study comprising participants free from mental illness at baseline. The study findings however need to be interpreted in light of the following limitations:

(i) the study sample comprised only men, therefore the results cannot be generalized to women; and (ii) our analyses focused on all types of psychotic disorders, since data on specific conditions such as schizophrenia and severe depression were not available.

In conclusion, GGT is associated with future risk of psychosis in a graded dose-response pattern in middle-aged Caucasian men. Serum GGT may have relevance for the prevention of psychosis; however, further research is needed to elucidate the mechanistic pathways underlying this association.

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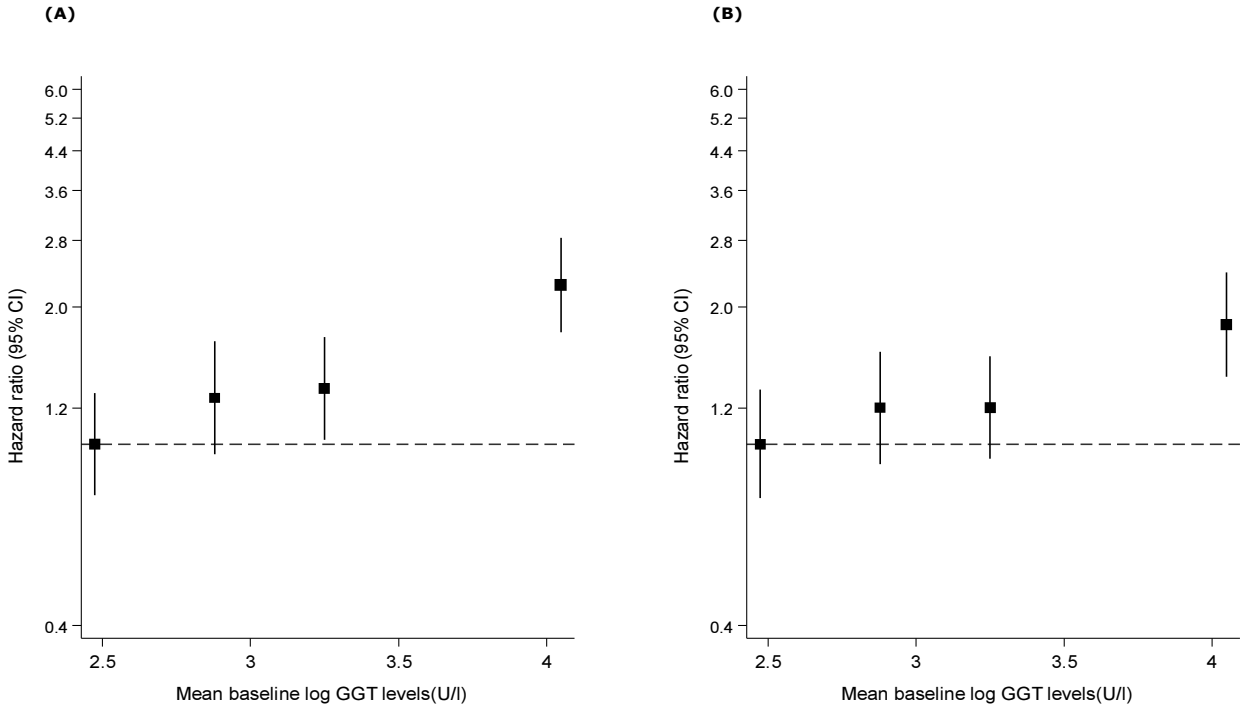
Figure legend

Figure. Hazard ratios for psychosis, by quartiles of baseline values of gamma-glutamyltransferase



A, adjusted for age; **B**, adjusted for age, plus body mass index, smoking status, history of diabetes, prevalent coronary heart disease, years of education, total cholesterol, and alcohol consumption

Table. Association of serum GGT and psychosis

Serum GGT (U/L)	Events/ Total	Model 1		Model 2		Model 3	
		HR (95% CI)	*P*-value	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Baseline GGT							
Per 1 SD increase	230 / 2,341	1.52 (1.34 to 1.73)	< 0.001	1.44 (1.25 to 1.66)	< 0.001	1.43 (1.24 to 1.65)	< 0.001
Q1 (5-15)	58 / 701	ref		ref		ref	
Q2 (16-20)	47 / 490	1.26 (0.86 to 1.86)	0.235	1.20 (0.81 to 1.77)	0.358	1.16 (0.79 to 1.72)	0.450
Q3 (21-33)	57 / 604	1.32 (0.92 to 1.91)	0.134	1.20 (0.82 to 1.75)	0.338	1.16 (0.79 to 1.69)	0.457
Q4 (≥ 34)	68 / 546	2.23 (1.57 to 3.17)	< 0.001	1.83 (1.24 to 2.69)	0.002	1.76 (1.19 to 2.60)	0.005
Usual GGT*							
Per 1 SD increase	230 / 2,341	1.84 (1.53 to 2.21)	< 0.001	1.70 (1.39 to 2.08)	< 0.001	1.67 (1.36 to 2.06)	< 0.001
Q1 (5-15)	58 / 701	ref		ref		ref	
Q2 (16-20)	47 / 490	1.40 (0.80 to 2.45)	0.235	1.30 (0.74 to 2.29)	0.358	1.24 (0.70 to 2.20)	0.450
Q3 (21-33)	57 / 604	1.50 (0.88 to 2.55)	0.134	1.31 (0.76 to 2.26)	0.338	1.23 (0.71 to 2.14)	0.457
Q4 (≥ 34)	68 / 546	3.20 (1.93 to 5.34)	< 0.001	2.40 (1.37 to 4.19)	0.002	2.26 (1.28 to 3.99)	0.005

CI, confidence interval; GGT, gamma-glutamyltransferase; HR, hazard ratio; ref, reference; Q, quartile; SD, standard deviation;
*, indicates correction for within-person variability in values of GGT, that is, the extent to which an individual's GGT measurements vary around a long-term average value ("usual GGT values"); 1 standard deviation higher $\log_e$ GGT is approximately equivalent to two-fold higher GGT values.

Model 1: Adjusted for age

Model 2: Model 1 plus body mass index, smoking status, history of diabetes, prevalent coronary heart disease, years of education, total cholesterol, and alcohol consumption

Model 3: Model 2 plus total energy intake, socioeconomic status, physical activity, and C-reactive protein